

It is claimed:

1. A method for preparing a spray-dried polyene powder suitable for oral inhalation to the lung, said method comprising:

5 (i) dissolving a polyene antifungal compound in an acidified solvent to form an acidic polyene-containing solution, and

(ii) spray drying said polyene-containing solution to form an inhaleable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than 60%.

10 2. The method of claim 1, wherein said dry powder produced in step (ii) contains no more than about 5% polyene degradation products.

3. The method of claim 1, wherein said solvent comprises acidified alcohol.

4. The method of claim 3, wherein said solvent comprises acidified methanol or ethanol.

5. The method of claim 1, wherein the pH of said acidified solution in step (i) ranges from about 3.5 to 5.

6. The method of claim 1, wherein the polyene is dissolved in said acidified solution to an extent greater than about 1 mg/ml.

7. The method of claim 6, wherein the polyene is dissolved in said acidified solution to an extent greater than about 2 mg/ml.

8. The method of claim 6, wherein the polyene is dissolved in said acidified solution to an extent greater than or equal to about 3 mg/ml.

9. The method of claim 1, wherein prior to said spray drying step, the acidic polyene-containing solution is maintained at a temperature below 25°C.

10. The method of claim 9, wherein prior to said spray drying step, the acidic polyene-containing solution is maintained at a temperature below about 8°C.

11. The method of claim 9, wherein the acidic polyene-containing solution comprising a feed solution is maintained at a temperature below 25°C during said spray drying step.

12. The method of claim 9, wherein the acidic polyene-containing solution comprising a feed solution is maintained at a temperature below 8°C during said spray drying step.

13. The method of claim 1, wherein said polyene comprises amphotericin or nystatin.

14. The method of claim 1, further comprising the step of dissolving a pharmaceutically acceptable excipient in said acidified solvent to form a solution comprising said excipient and said polyene.

15. The method of claim 14, wherein said excipient is leucine or trileucine.

16. The method of claim 1, wherein said polyene-containing solution comprises dissolved solids and wherein at least about 60% by weight of the dissolved solids comprises said polyene.

17. The method of claim 16, wherein at least about 70% by weight of the dissolved solids comprises said polyene.

18. The method of claim 17, wherein said polyene-containing solution is substantially absent additional excipients or stabilizers.

19. The method of claim 1, wherein said polyene-containing solution is absent lipid or polymeric encapsulating agents.

20. The method of claim 1, wherein said inhaleable dry powder comprises particles characterized by a MMAD of less than about 5 microns.

21. A method for preparing a spray-dried polyene powder suitable for oral inhalation to the lung, said method comprising:

- (i) suspending a polyene antifungal compound in an aqueous solvent to form a suspension,
- (ii) wet milling the suspension from (i) to form a wet-milled suspension, and
- (iii) spray drying the wet milled suspension to produce an inhaleable dry powder containing no more than about 10% polyene degradation products and characterized by an emitted dose greater than about 60%.

22. The method of claim 21, wherein said wet milling step comprises homogenizing to form a homogenized suspension.

23. The method of claim 21, wherein said aqueous solvent in step (i) further comprises an excipient.

24. The method of claim 21, further comprising mixing the wet milled suspension in step (ii) with either a solid excipient or an aqueous solution comprising an excipient prior to spray drying.

25. The method of claim 23 or claim 24, wherein said excipient is selected from the group consisting of leucine, trileucine, and buffers.

26. The method of claim 25, wherein said excipient is a buffer that is sodium citrate or sodium phosphate.

27. The method of claim 21, further comprising the step of exposing the powder to moisture
5 either during or after said spray drying.

28. The method of claim 27, comprising the step of exposing the powder formed in step (iii) to moisture in an amount effective to provide a powder having a moisture content ranging from about 4% to about 10% by weight.

29. The method of claim 27, wherein said spray drying step further comprises spray drying said suspension using a drying gas comprising an amount of water sufficient to form a spray dried powder having a moisture content ranging from about 4% to about 10% by weight.

30. The method of claim 27, wherein said exposing step comprises exposing or maintaining the powder at a relative humidity above about 10%.

31. The method of any one of claims 27-30, wherein said exposing step is effective to reduce the MMAD of the spray dried powder from that of a spray dried powder prepared in the absence of said exposing step.

32. The method of claim 21, wherein the concentration of said polyene in the suspension in step (i) ranges from about 1 mg/mL to about 100 mg/mL.

33. The method of claim 32, wherein the concentration of said polyene in the suspension in step (i) ranges from about 5 mg/mL to about 20 mg/mL.

34. The method of claim 21, further comprising the step of aerosolizing the dry powder formed in step (iii).

35. The method of claim 27, further comprising, after said exposing step, aerosolizing the dry powder formed in (iii).

5 36. The method of claim 21, wherein the inhaleable dry powder formed in step (iii) is further characterized by an MMAD of less than about 5 microns.

37. The method of claim 27, wherein the inhaleable dry powder, after exposure to moisture, is further characterized by an MMAD of less than about 5 microns.

10 38. The method of claim 37, wherein the inhaleable dry powder, after exposure to moisture, is further characterized by an MMAD of less than about 3.5 microns.

39. The method of claim 21, wherein said polyene is amphotericin or nystatin.

40. A dry powder produced by the method of claim 1.

41. A dry powder produced by the method of claim 21.

20 42. A spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound, wherein the composition comprises no more than about 10% polyene degradation products and is characterized by an emitted dose greater than about 60%.

25 43. The powder composition of claim 42, containing no more than about 5% polyene degradation products.

44. The powder composition of claim 42, wherein the powder comprises particles having an MMAD of less than about 5 microns.

45. The powder composition of claim 44, wherein the powder comprises particles having an MMAD of less than about 3.5 microns.

5 46. The powder composition of claim 42, which is non-proteinaceous.

47. The powder composition of claim 42, wherein said polyene is nystatin or amphotericin B.

10 48. The powder composition of claim 42, wherein said polyene is non- encapsulated.

49. The powder composition of claim 48, wherein said polyene is non-liposome or non-polymer encapsulated.

50. The powder composition of claim 42 substantially comprising neat polyene.

51. The powder composition of claim 42, further comprising a pharmaceutically acceptable excipient.

52. The powder composition of claim 51, wherein said excipient is selected from the group consisting of buffers, leucine, and trileucine.

53. The powder composition of claim 51, comprising at least about 30% by weight polyene.

25 54. The powder composition of claim 53, comprising at least about 50% by weight polyene.

55. The powder composition of claim 42, having a water content greater than about 4% by weight.

56. The powder composition of claim 55, having a water content ranging from about greater than 4% by weight to about 10% by weight.

57. A spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound and a leucyl-containing excipient comprising from 1 to 3 amino acid residues.

58. An aerosolized, spray-dried powder composition suitable for oral inhalation to the lung comprising a therapeutically effective amount of a polyene antifungal compound, wherein the composition comprises no more than about 10% polyene degradation products and is characterized by an emitted dose greater than about 60%.

59. A method for treating or preventing fungal infection in a subject in need thereof, said method comprising administering to said subject by oral inhalation a therapeutically effective amount of a spray dried powder composition of claim 42 in aerosolized form.

60. In a method for preparing an inhaleable spray-dried powder comprising the steps of spray drying a solution or suspension containing an active agent to form particles having a particular MMAD, the improvement comprising exposing said powder either during or after spray drying to moisture in an amount effective to reduce the MMAD of the particles from that of the particles formed in the absence of said exposing step.